A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after Final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on June 24, 2011 has been entered.

EXAMINER'S AMENDMENT

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicants, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this Examiner's Amendment was given in a telephone interview with B. Aaron Shulman on March 21, 2012.

In the claims:

Claims 20 and 23 are canceled.

In claim 9, lines 2-3, "said pharmaceutical composition of the invention comprises between 50 and 100 mg" is deleted and -- the amount -- is inserted therefor. At the end of the claim, following "adults," -- is from 50 to 100 mg -- is inserted.

In claim 10, line 2, "said pharmaceutical composition comprises between 1 and 8 mg" is deleted and -- the amount -- is inserted therefor. At the end of the claim, following "adults," -- is from 1 to 8 mg -- is inserted.

In claim 11, line 2, "said pharmaceutical composition comprises between 2 and 8 mg" is deleted and -- the amount -- is inserted therefor. At the end of the claim, following "adults," -- is from 2 to 8 mg -- is inserted.

In claim 12, line 2, "said pharmaceutical composition comprises between 1 and 4 mg" is deleted and -- the amount -- is inserted therefor. At the end of the claim, following "adults," -- is from 1 to 4 mg -- is inserted.

In claim 13, line 2, "said combination comprises" is deleted. On line 3, -- are -- is inserted following "granisetron."

In claim 15, line 2, "comprising" is deleted and -- consisting essentially of -- is inserted therefor.

In claim 21, line 1, "20" is deleted and -- 1 -- is inserted therefor. On lines 1-2, the term "comprising" is deleted and -- consisting essentially of -- is inserted therefor.

In claim 22, line 1, "20" is deleted and -- 1 -- is inserted therefor. On lines 1-2, the term "comprising" is deleted and -- consisting essentially of -- is inserted therefor.

In claim 24, lines 1-2, "A" is deleted and -- The -- is inserted therefor. Following "composition" -- of claim 5, consisting essentially of -- is inserted and "comprising" is deleted.

In the **title**: The first word, i.e., "New" is deleted.

In the **Abstract**: The content of the Abstract is deleted and --

The present invention concerns combinations of an anti-emetic agent and an enkephalinase inhibitor for use in methods for treating diarrhea and/or gastroenteritis. -- is inserted.

REASONS FOR ALLOWANCE

A Response filed June 24, 2011 is acknowledged in which claims 1 and 5-25 remained under consideration. Additionally, a Declaration by Dr. Jeanne-Marie Lecomte under Rule 132, filed June 24, 2011, is further acknowledged and is found persuasive.

Claims 1 and 5-24 remained rejected under 35 U.S.C. 103(a) as being unpatentable over Cojocaru et al., Archives Pediatrics, in view of Cubeddu et al.,

Alimentary Pharmacol. Ther., and Boige et al., Bulletin du Cancer, in the last Office Action. It was asserted Cojocaru teaches the administration of racecadotril in the treatment of diarrhea. Racecadotril is an inhibitor of enkephalins (endogenous opioid peptides) that causes a reduction in intestinal secretion. As an optical isomer of racecadotril, it would have been reasonable to expect dexecadotril to exhibit similar pharmacologic properties. Cubeddu teaches the administration of the 5-HT3 receptor antagonist ondansetron, as an antiemetic in the treatment of gastroenteritis. Boige teaches the administration of ondansetron, granisetron and racecadotril to treat nausea, vomiting and diarrhea. See the discussions under Prevention et traitement specifiques and Diarrhee. Nausea, vomiting and diarrhea frequently occur following the administration of various cancer chemotherapeutic agents and regimens. Boige teaches an oral dosage of granisetron to be 1 mg every 12 hours, an oral dosage of ondansetron to be 8 mg every 8 hours and an intravenous dosage of ondansetron to be 32 mg. Additionally, dosages based on mg/kg body weight are provided. The specific enkephalinase inhibitor acetorphan, which is racecadotril, at a dosage of 300 mg/day, is specifically indicated in late-onset diarrhea.

In the Declaration Dr. Lecomte states:

Racecadotril and dexecadotril exhibit a strong anti-secretory effect in that they substantially facilitate the reabsorption of water and salts from the intestinal lumen and thereby inhibit the associated loss of water and salts in diarrheic patients. However, these agents may induce an acceleration of the intestinal transit. This acceleration tends to limit the anti-secretory effects of these drugs inasmuch as the reabsorption process has not time enough to fully develop in the intestinal lumen. It is also a possible undesirable side effect of racecadotril.

It was shown in the previously filed declaration that co-administration of racecadotril with granisetron surprisingly suppresses this side effect of racecadotril and hence potentiates the anti-diarrheal activity of racecadotril in mice.

This result shows that the side effect of racecadotril may be prevented by granisetron. There was no suggestion that granisetron would slow down the increase of intestinal transit caused by racecadotril. This combination is thus unobvious.

In response to the rejection of record under 35 U.S.C. 103, Dr. Lecomte states:

Boige merely describes the administration of ondansetron to treat emesis and the administration of racecadotril to treat diarrhea. Boige does not suggest combining these substances to suppress the side effect of racecadotril and thereby potentiate the antidiarrheal effect of the latter. Ondansetron is an anti-emetic agent and does not possess anti-diarrheic activity. Rather, it was found to increase the occurrence of diarrheal episodes. Cubbedu shows that the administration of ondansetron increases the number of diarrheal episodes, compared to a placebo.

The rejection of record of claims 1 and 5-25 under 35 U.S.C. 103(a), as being unpatentable over Cojocaru et al., Archives Pediatrics, in view of Cubeddu et al., Alimentary Pharmacol. Ther., and Boige et al., Bulletin du Cancer, is withdrawn. The co-administration of ondansetron with dexecadotril suppresses the increase in the intestinal transit induced by dexecadotril, while reducing the number and duration of diarrheic stools. Ondansetron does not possess anti-diarrheal activity.

The potentiation of the anti-diarrheal activity of dexecadotril when combined with ondansetron illustrates an unexpected result following the administration of these two compounds. Accordingly, claims 1, 5-19, 21, 22, 24 and 25 are allowed in view of the contemporary knowledge of the art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Jeff Lundgren, can be reached 571-272-5541.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 21, 2012

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1629